

Appendix D: Driver genes detected in preinvasive lesions. Includes clonal/subclonal classification and FATTHM-MKL scores

Gene	Function	Functional category	P106 LLL	P119 LMB	142 RMB	145 SL	P149 LUL/LLL	P149 RLL	152 RIB	152 LMB
Clonal 'driver' mutations shared between ≥1 patient										
CTNNA2	Cell to cell adhesion	Cell adhesion	0.994			0.947				
CTNND2	Cell to cell adhesion	Cell adhesion		0.988			0.985			
TP53	Widespread tumour suppression function	Cell death	0.991	0.98	0.989		0.02	0.947	0.285	0.285
BIRC6	Cell death regulation	Cell death	0.993					N/A		
CSMD3	Negative regulator airway epithelium proliferation	Cell division	0.982	0.922	0.929		0.947			
CDKN2A	Cell cycle arrest	Cell division	Deletion		0.976					
BRCA2	DNA damage repair	DNA repair	0.285			0.668				
TFEB	Transcription factor	Gene transcription/translation			0.963			0.975		
MUC16	Epithelial protection	Tissue homeostasis/repair	0.007		0.019				0.009	
Clonal 'driver' mutations unique to each patient										
FAT3	Cell to cell adhesion	Cell adhesion	0.963							
CSF3R	Cell to cell adhesion	Cell adhesion	0.794							
MB21D2	Cell to cell adhesion	Cell adhesion			0.992					

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FAT1	Cell to cell adhesion	Cell adhesion					N/A			
DCC	Cell to cell adhesion	Cell adhesion					0.994			
LARP4B	Activates apoptosis	Cell death	0.882							
PCM1	Anchoring microtubules during cell division	Cell division	0.998							
CCNE1	Cell cycle protein	Cell division		0.964						
CDC73	Cell cycle repressor	Cell division			0.989					
CDKN2C	Cell cycle arrest	Cell division			0.938					
NUTM1	Cell proliferation	Cell division							N/A	
PDE4DIP	Cell division	Cell division	N/A							
JAK2	Tyrosine kinase	Cell signalling/transport							0.946	0.946
SOCS1	Suppresses cytokine signalling	Cell signalling/transport	0.835							
ROS1	Receptor tyrosine kinase	Cell signalling/transport		0.934						
SUFU	Negatively regulates the hedgehog signalling pathway	Cell signalling/transport	0.994							
ECT2L	Regulates guanosine triphosphate activity	Cell signalling/transport			Deletion					

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<i>FGFR4</i>	Growth factor receptor	Cell signalling/transport			0.982					
<i>PTPRC</i>	Regulate T Cell signalling/transport	Cell signalling/transport				0.992				
<i>RGS7</i>	Deactivates G proteins	Cell signalling/transport				0.987				
<i>NOTCH2</i>	Tissue repair	Cell signalling/transport					0.961			
<i>ACVR1B</i>	TGF-beta signalling	Cell signalling/transport					0.942			
<i>DDR2</i>	DNA damage repair	DNA repair			0.883					
<i>RAD21</i>	DNA damage repair	DNA repair			0.962					
<i>BRCA1</i>	DNA damage repair	DNA repair		0.67						
<i>MYH9</i>	Cell motility	EMT							N/A	
<i>SETD1B</i>	Modify chromatin architecture	Epigenetics					0.889			
<i>KMT2A</i>	Modify chromatin architecture	Epigenetics					0.995			
<i>ARID1A</i>	Modify chromatin architecture	Epigenetics							0.94	
<i>KDM5A</i>	Modify chromatin architecture	Epigenetics								0.963
<i>KMT2C</i>	Modify chromatin architecture	Epigenetics								0.961
<i>BCAS3</i>	Modify chromatin architecture	Epigenetics		0.964						

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<i>RSBN1L</i>	Modify histone architecture	Epigenetics		0.563						
<i>EP300</i>	Modify chromatin architecture	Epigenetics			0.961					
<i>KAT6A</i>	Modify chromatin architecture	Epigenetics					0.957			
<i>DEK</i>	Modify chromatin architecture	Epigenetics					0.934			
<i>MN1</i>	Transcription factor co-activator	Gene transcription/translation	0.882							
<i>USP8</i>	Post translational ubiquitination to mark molecules for degradation	Gene transcription/translation		0.998						
<i>TCF12</i>	Transcription factor	Gene transcription/translation		0.995						
<i>TLX3</i>	Transcription factor	Gene transcription/translation		0.898						
<i>HOXA11</i>	Transcription factor	Gene transcription/translation			0.884					
<i>NFKB2</i>	Transcription factor for inflammation genes	Gene transcription/translation			0.586					
<i>CBLB</i>	Post translational ubiquitination to mark molecules for degradation	Gene transcription/translation					0.985			

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NCOA2	Transcription factor co-activator	Gene transcription/translation				0.889				
CREBBP	Transcription factor co-activator	Gene transcription/translation					0.978			
BCL9	Transcription factor co-activator	Gene transcription/translation				0.963				
PAX8	Transcription factor	Gene transcription/translation					0.998			
GRM3	Glutamate receptor	Metabolism							0.99	0.99
RSPO3	Activates angiogenesis	Metabolism							0.751	0.751
FBXW7	Subunit of proteosome	Metabolism		0.928						
COL1A	Collagen type 1	Tissue homeostasis/repair				0.974				
Clonal 'driver' mutations unique to each patient with FATHMM score ≤5										
OMD	Cell to cell adhesion	Cell adhesion	0.294							
ZNF471	Cell division	Cell division		0.019						
TERT	Maintains telomere length	Cell division			0.073					
ITK	T cell intracellular tyrosine kinase	Cell signalling/transport	0.051							
CNBD1	cAMP signalling	Cell signalling/transport			0.262					
TPM4	Cytoskeletal contractile system protein	EMT					0.41			

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ARID1B	Modify chromatin architecture	Epigenetics	0.045							
A1CF	Post transcriptional modification	Gene transcription/translation					0.064			
ZNF479	Transcription factor co-activator	Gene transcription/translation					0.432			
Subclonal 'driver' mutations shared between ≥ 1 patient										
TP53	Widespread tumour suppression function	Cell death				0.299		0.647	0.285	
CSMD3	Negative regulator cell proliferation airway epithelium	Cell division		0.913			0.993		0.957	
NUP214	Traffic molecules between cytoplasm and nucleus	Cell signalling/transport						0.141	0.947	
TAP1	Antigen transport	Cell signalling/transport			0.989			0.974		
STAT5B	Cell signalling	Cell signalling/transport				0.998	0.997			
FAT4	Maintains cell polarity	EMT			0.989			0.981		
AFF3	Transcription factor co-activator	Epigenetics				0.926		0.969		
RGPD3	Post translational ubiquitination to	Gene transcription/translation			0.971			0.972		

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	mark molecules for degradation									
NOTCH1	Tissue repair	Tissue homeostasis/repair	0.975					0.961		
MUC16	Epithelial protection	Tissue homeostasis/repair					0.013	0.009	0.08	
Subclonal 'driver' mutations unique to each patient with FATHMM score ≥ 5 or FATHMM score N/A										
FAT1	Cell to cell adhesion	Cell adhesion						0.94		
STRN	Negative regulator cell proliferation	Cell division				0.992				
LRP1B	Negative regulator cell proliferation	Cell division				0.957				
XPO1	Cell cycle	Cell division						0.954		
NPM1	Cell division	Cell division			0.957					
MAP2K2	Activate cell division pathways	Cell division	0.8							
CDK6	Cell cycle	Cell division						0.852		
STIL	Chromosome segregation	Cell division						0.959		
RGS7	Deactivates G proteins	Cell signalling/transport					0.988			
LATS2	Protein kinase (adds phosphate)	Cell signalling/transport						0.898		
PREX2	Regulates guanosine triphosphate activity	Cell signalling/transport						0.991		
PICALM	Endocytosis	Cell signalling/transport						0.96		

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<i>DNM2</i>	Endocytosis	Cell signalling/transport						0.993		
<i>BCR</i>	Kinase activity	Cell signalling/transport			0.871					
<i>APC</i>	Antagonist of Wnt signalling	Cell signalling/transport				0.784				
<i>NBEA</i>	Protein kinase (adds phosphate)	Cell signalling/transport					0.995			
<i>CARD11</i>	NFKB signalling (immune pathways)	Cell signalling/transport						0.982		
<i>CACNA1D</i>	Calcium channel	Cell signalling/transport						0.973		
<i>KCNJ5</i>	Potassium channel	Cell signalling/transport						0.995		
<i>FGFR3</i>	Growth factor receptor	Cell signalling/transport						0.984		
<i>PTPRK</i>	Protein phosphatase (remove phosphate)	Cell signalling/transport						0.978		
<i>PTPRD</i>	Protein phosphatase (remove phosphate)	Cell signalling/transport						0.983		
<i>SUFU</i>	Negatively regulates the hedgehog signalling pathway	Cell signalling/transport						0.881		

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WNK2	Protein kinase	Cell signalling/transport							0.936	
CLTCL1	Endocytosis	Cell signalling/transport							0.936	
TSC2	Negatively regulate mTORC signalling	Cell signalling/transport								0.945
ANK2	Ion transport	Cell signalling/transport								0.933
PTEN	Blocks PI3K signaling	Cell signalling/transport					N/A			
ATM	Protein kinase (adds phosphate)	Cell signalling/transport						N/A		
ATR	DNA damage sensor	DNA repair					N/A	0.974		
MSH6	DNA damage repair	DNA repair						0.886		
SETBP1	DNA replication	DNA replication								N/A
TRRAP	Modify chromatin architecture	Epigenetics						0.991		
BCL11A	Modify chromatin architecture	Epigenetics						0.987		
KMT2A	Modify chromatin architecture	Epigenetics						0.955		
SETD2	Modify chromatin architecture	Epigenetics		0.987						
PBRM1	Modify chromatin architecture	Epigenetics						0.976		
ARID2	Modify chromatin architecture	Epigenetics						0.985		

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EP300	Modify chromatin architecture	Epigenetics								0.993
ASXL2	Modify chromatin architecture	Epigenetics							0.809	
ARID1B	Modify chromatin architecture	Epigenetics							N/A	
NFE2L2	Transcription factor	Gene transcription/translation		0.996						
HIF1A	Transcription factor	Gene transcription/translation		0.922						
PRDM1	Transcription repressor	Gene transcription/translation		0.95						
CARS	Gene translation machinery	Gene transcription/translation		0.632						
MED23	Transcription factor co-activator	Gene transcription/translation			0.989					
WWTR1	Transcription factor co-activator	Gene transcription/translation				0.741				
MECOM	Transcription factor co-activator	Gene transcription/translation						0.903		
FUBP1	Transcription factor co-activator/repressor	Gene transcription/translation						0.983		
PABPC1	Transcription regulation	Gene transcription/translation						0.968		
TLX1	Transcription factor	Gene transcription/translation						0.982		
NKX2-1	Transcription factor	Gene transcription/translation						0.994		

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CIC	Transcription repressor	Gene transcription/translation						0.7		
BCL3	Transcription factor co-activator	Gene transcription/translation							0.947	
RNF213	Post translational ubiquitination	Gene transcription/translation								0.987
NOS2	Nitric oxide production	Metabolism								0.829
TFRC	Iron uptake	Metabolism	0.978							
COL3A1	Type III collagen	Tissue homeostasis/repair					0.926			
Subclonal 'driver' mutations unique to each patient with FATHMM score ≤5										
CD70	Cytokine that proliferates T cells	Cell signalling/transport				0.45				
NUP210L	Traffic molecules between cytoplasm and nucleus	Cell signalling/transport						0.28		
ZNF479	Transcription factor co-activator	Gene transcription/translation					0.432			
ELL	RNA polymerase machinery	Gene transcription/translation						0.107		
ZNF471	Transcription factor co-activator	Gene transcription/translation						0.003		
IKZF1	Transcription factor	Gene transcription/translation			0.448					
POLG	Mitochondrial DNA polymerase pathway	Metabolism							0.068	

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<i>PDSS2</i>	Mitochondrial ATP production	Metabolism						0.094		
Late 'driver' subclonal mutations in progressive lesions with FATHMM score ≥ 5 or FATHMM score N/A										
<i>CTNNA2</i>	Cell to cell adhesion	Cell adhesion				0.947				
<i>CSF3R</i>	Neutrophil adhesion	Cell adhesion				0.754				
<i>DCC</i>	Cell to cell adhesion	Cell adhesion							0.988	
<i>BIRC6</i>	Cell death regulation	Cell death				N/A				
<i>PDE4DIP</i>	Cell division	Cell division				N/A				
<i>MAP2K2</i>	Activate cell division pathways	Cell division				0.8				
<i>LRP1B</i>	Negative regulator cell proliferation	Cell division							0.877	
<i>PTEN</i>	Blocks PI3K signaling	Cell signalling/transport	0.946							
<i>NUP214</i>	Traffic molecules between cytoplasm and nucleus	Cell signalling/transport				0.953				
<i>SUFU</i>	Negatively regulates the hedgehog signalling pathway	Cell signalling/transport				0.994				
<i>TNC</i>	Cell migration	EMT				0.974				
<i>RSBN1L</i>	Modify chromatin architecture	Epigenetics			0.99					

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<i>TBX3</i>	Transcription factor	Gene transcription/translation	0.969							
<i>MYOD1</i>	Transcription factor	Gene transcription/translation							0.755	
Gene	Function	Functional category	P106 LLL	P119 LMB	142 RMB	145 SL	P149 LUL/LLL	P149 RLL	152 RIB	152 LMB
<i>CYP2C8</i>	Cytochrome P450 enzyme: xenobiotic metabolism	Metabolism				0.84				
<i>SDHA</i>	Mitochondrial ATP production	Metabolism					0.992			
<i>NOTCH1</i>	Tissue repair	Tissue homeostasis/repair				0.985				
Late 'driver' subclonal mutations in progressive lesions with FATHMM score ≤ 5										
<i>SPECC1</i>	Cell division	Cell division				0.319				
<i>ITK</i>	T cell intracellular tyrosine kinase	Cell signalling/transport				0.051				
<i>MUC16</i>	Epithelial protection	Tissue homeostasis/repair				0.061				